Emerging trends – Biocompatibility Insights from Copenhagen ‘22, Annapolis ‘23 and Copenhagen’24, and '26, with a view forward



Ron Brown

Risk Science Consortium



Themes discussed at the meeting in Annapolis in 2023

- Need for an evidence-based approach for the safety assessment of devices.
- Need to improve the process to validate and qualify new approaches for regulatory use.
- Need to streamline the preclinical biocompatibility assessment of devices and make the assessed endpoints and test methods more clinically relevant.

Have we made progress to address these issues?



Themes discussed at the meeting in Annapolis in 2023

- **Need for an evidence-based approach for the safety assessment of devices.**
- **Need to improve the process to validate and qualify new approaches for regulatory use.**
- **Need to streamline the preclinical biocompatibility assessment of devices and make the assessed endpoints and test methods more clinically relevant.**

Have we made progress to address these issues?

The principles of evidence-based medicine serve as the foundation for evidence-based toxicology

What is Evidence Based Medicine?

Evidence-based medicine (EBM) uses the scientific method to organize and apply current data to improve healthcare decisions. Thus, the best available science is combined with the healthcare professional's clinical experience and the patient's values to arrive at the best medical decision for the patient.

Tenney and Varacello (2022) StatPearls
https://www.ncbi.nlm.nih.gov/books/NBK430685/

Food for Thought ... on Evidence-Based Toxicology

Thomas Hartung

Johns Hopkins University, Bloomberg School of Public Health, Dept. Environmental Health Sciences, Doerenkamp-Zbinden Chair for Evidence-based Toxicology, Center for Alternatives to Animal Testing, Baltimore, USA

ALTEX (2009) 26(2):75-82.

Box 2

10 defining characteristics of EBT

- promotes the consistent use of transparent and systematic processes to reach robust conclusions and sound judgments
- addresses societal values and expectations and is socially responsible
- displays a willingness to check the assumptions upon which current toxicological practice is based to facilitate continuous improvement
- recognises the need to provide for the effective training and development of professional toxicologists
- acknowledges a requirement for new and improved tools for critical evaluation and quantitative integration of scientific evidence
- embraces all aspects of toxicological practice, and all types of evidence of which use is made in hazard identification, risk assessment and retrospective analyses of causation
- ensures the generation and use of best scientific evidence
- includes all branches of toxicological science: human health assessment, environmental and ecotoxicology and clinical toxicology
- acknowledges and builds upon the achievements and contributions of Evidence Based Medicine/Evidence Based Health Care
- fosters the integration of expert judgment with best possible external evidence

Your Full-Service Partner for Immuno-Oncology Drug Discovery
Learn More

ADVERTISEMENT

Feedback



Webinar

Time for a Change: Evidence-Based Approaches for the Biological Safety Assessment of Medical Devices

In this webinar, Ron Brown discusses the problems with current medical device biological safety assessment approaches and suggests that evidence-based strategies could be the solution.

THE UNIVERSITY OF CHICAGO
MARINE BIOLOGICAL LABORATORY

How can we implement an Evidence-Based Approach for the Biological Safety Assessment of Medical Devices?

2025 Friday Evening Lectures



June 13 - "Staying True to the Indispensable Values of Science"

E.B. Wilson History and Philosophy of Science Lecture

Holden Thorp, Editor-in-Chief, *Science* Magazine

WATCH THE THORP VIDEO

VIEW THORP EVENT INFO

"do the best science we can"

Example of doing the best science

Review Article

Material-Mediated Pyrogens in Medical Devices: Myth or Reality?

Lindsey K. Borton[1] and Kelly P. Coleman[2]

[1]Gradient, Boston, MA, USA; [2]Medtronic, Minneapolis, MN, USA

Lindsey Borton (Gradient) and Kelly Coleman (Medtronic) received the 2026 Lush Prize for their efforts to show that testing medical devices for material-medical pyrogenicity using the Rabbit Pyrogen Test is not necessary



Is doing the best science enough?

Using the best science is good start, but it's not enough.

"We will just out science them. We will make the science so evident that it will be impossible for them to reject it."

This is the most naïve thing I've ever said.



Is doing the best science enough?



Kelly Coleman, NABS poster, September, 2026

- The results of the ISO/TC 194 WG8-sponsored in vitro irritation round robin study, which involved 24 global laboratories, 2,000 blinded samples, and EpiDerm and SkinEthic RHE tissues, where published in 2018 and the ISO 10993-23 standard went into effect in July of 2021.

- ISO 10993-23:2021's Clause 4 states: "In vitro irritation test shall be performed before animal testing, or human patch test is considered."

- In 2020, a follow-up paper comparing in vitro and in vivo results was published, and in the 2022 a second follow-up report was published about in vitro irritation testing of mild irritants.

RECOGNITION OF ISO 10993-23:2021

Asia	Europe	CEN & EU	CEN & EU	CEN & EU	CEN & EU	CEN & EU	CEN Affiliates
China	Austria	Denmark	Hungary	Luxembourg	N. Macedonia	Sweden	Albania
Japan	Belgium	Estonia	Iceland	Malta	Romania	Switzerland	Bosnia and
	Bulgaria	Finland	Ireland	Netherlands	Serbia	Turkey	Herzegovina
	Croatia	France	Italy	Norway	Slovakia	U.K.	Montenegro
	Cyprus	Germany	Latvia	Poland	Slovenia		
	Czech Rep.	Greece	Lithuania	Portugal	Spain		

Kelly Coleman, Update to TC194 WG8, 2022

As of October 2025:

- 191 of the UN's 193 Member States (**99%**) accept in vitro irritation data.
- **95%** of humanity lives in those 191 countries.
- Recognition by the US and Canada is pending.

Kelly Coleman, NABS poster, September, 2026

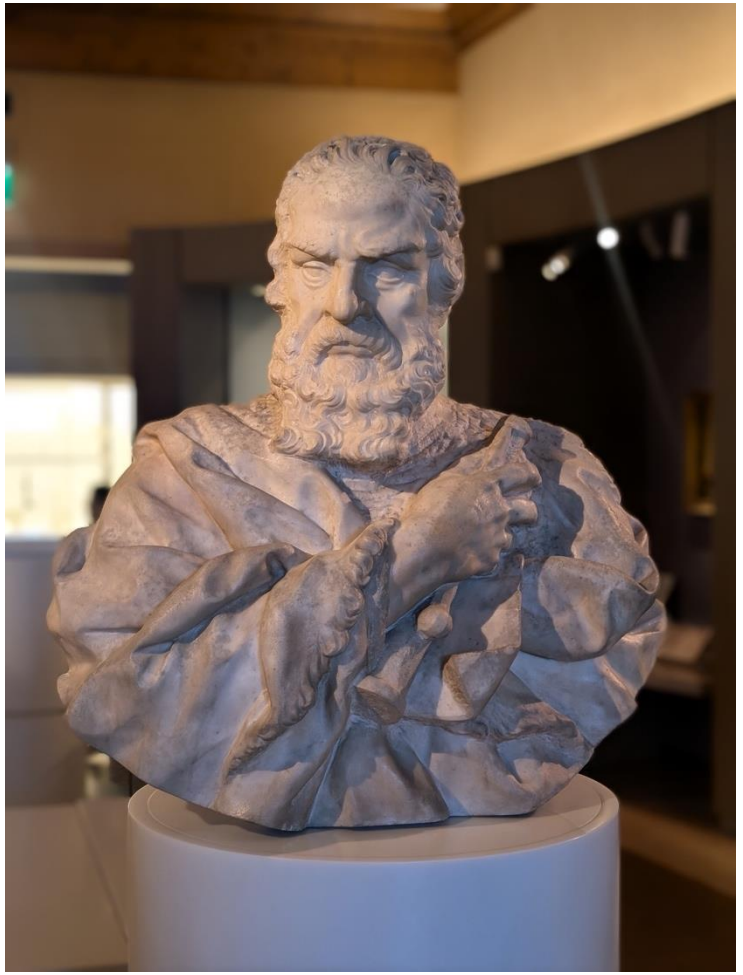
How do we address regulatory reluctance to accept evidence-based approaches?

1. Do the best science and communicate it. Present and discuss the issues at meetings like this one.

2. Examine each 10993 standard for recommendations that are made on the basis of conservative default assumptions or unvalidated legacy test methods, not data.

3. In the face of overwhelming scientific evidence, require an explanation from the opponents to change why they support of the status quo. It should no longer be acceptable to support a method or policy based on the justification, "That's the way we've always done it."

How can we implement an Evidence-Based Approach for the Biological Safety Assessment of Medical Devices?



Challenge the status quo

"What do you have to say about the principal philosophers of this academy who are filled with the stubbornness of an asp and do not want to look at either the planets, the moon or the telescope…?"

Galileo

How can we implement an Evidence-Based Approach for the Biological Safety Assessment of Medical Devices?

This raises the question, "How much data are needed to move from the status quo?"

When is a new method considered to be validated and qualified for regulatory use?

Does the best method consider clinical relevance?

FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal use in testing when feasible…We will consider if such an alternative method could be assessed for equivalency to an animal test method.

CDRH (2023) Biocompatibility Guidance Document

Would regulatory acceptance of new methods be facilitated by development of a best practices roadmap that we all agree to?



Themes discussed at the meeting in Annapolis in 2023

- Need for an evidence-based approach for the safety assessment of devices.
- Need to improve the process to validate and qualify new approaches for regulatory use.
- Need to streamline the preclinical biocompatibility assessment of devices and make the assessed endpoints and test methods more clinically relevant.

Have we made progress to address these issues?

Need to improve the process to validate and qualify new approaches for regulatory use

1. It would help to have a validation and qualification roadmap to ensure that all WGs and stakeholders use a consistent practice when validating and qualifying NAMs.

2. We also need a new way of thinking:

   - identify the best tool for the job, not how can a NAM replace an existing test method.

   - develop a collaborative innovation mindset among all stakeholders.



Themes discussed at the meeting in Annapolis in 2023

- Need for an evidence-based approach for the safety assessment of devices.
- Need to improve the process to validate and qualify new approaches for regulatory use.
- Need to streamline the preclinical biocompatibility assessment of devices and make the assessed endpoints and test methods more clinically relevant.

Have we made progress to address these issues?

Approaches to streamline the biocompatibility evaluation process

- Is it necessary to assess all of the currently recommended biocompatibility effects for each device?
- Is it necessary to use biocompatibility test methods to assess biological endpoints that take weeks or months to complete when more efficient/predictive tests are available?
- Is it necessary to conduct tests just to satisfy regulatory expectations, especially for low-risk devices?

The changes made to ISO 10993-1:2025 will be essential for implementing these changes in mindset.

Do we need to evaluate all devices for all endpoints?



Is there a need to evaluate all devices for skin sensitization potential?

A streamlined approach doesn't always work

frontiers | Frontiers in Medical Technology

TYPE Perspective
PUBLISHED 28 November 2022
DOI 10.3389/fmedt.2022.1006984

A case study: Re-evaluating the biological risk following a processing aid change on a marketed cardiovascular implant device

Frances K. Hsia*, Alessia Stornetta and Nicole V. Soucy

Global Toxicology and Biocompatibility, Preclinical Sciences, Boston Scientific Corporation, Arden Hills, MN, United States

This case study highlights the recent shift in regulatory expectations around chemical characterization and questions the **value of additional biological testing when faced with low extractable levels of low toxicity concern.**

It also demonstrates the need to hold to key portions of the ISO 10993 risk management framework to **avoid excessive burden on medical device development when there is little to no determined risk to patient safety.**

Can we reach the same biocompatibility conclusions using a smarter, streamlined, and less burdensome approach?

Additional suggestions to streamline the biocompatibility evaluation process

Frontloading toxicology

Use a tiered approach based on a limited battery of biocomp tests early in the R&D process of a device

NAMs+

Use of NAMs in a weight-of-evidence approach to facilitate the regulatory acceptance of the new method.

What do we means by frontloading toxicology?

Problem: We often rely solely on testing of the final, finished device

The current FDA expectation is that testing should be conducted of the final finished device:

> ***The risk assessment should evaluate the final finished device. The Agency makes a clearance or approval decision for a medical device as it is supplied in its final finished form. The Agency does not clear or approve individual materials that are used in the fabrication of medical devices.***
>
> **CDRH (2023) Biocompatibility Guidance Document**

Too often, when the device is only tested only at the final, finished stage, biocompatibility issues may only be detected late in the device development process.

Proposed solution

De-risk materials by frontloading testing in a tiered approach

- Ideally, we should provide engineers with a suite of materials that are not only functional but also meet safety requirements.
- Frontloading a minimum suite of biocomp tests early in the R&D process could avoid downstream surprises.
- Regulatory agencies will still want to see testing done on the final, finished device, but frontloading testing may be one way to avoid downstream headaches.
- This approach may also avoid the need to repeat costly and time consuming biocomp tests like skin sensitization or chemical characterization.

What do we mean by NAMs+?

Problem 1: The ability to waive biocompatibility testing requirements based solely on information on the materials of construction of the device has not been universally accepted by some regulatory agencies.

Problem 2: Similarly, the use of NAMs has not been universally accepted by regulatory agencies for the safety assessment of medical devices.

Can these two approaches be used in a weight-of-evidence approach to provide the necessary justification to not perform testing?


REGULATORY ACCEPTANCE
SAFETY PATH
Material Characterization
#749
NAMS
#750


REGULATORY ACCEPTANCE
SAFETY PATH
FINISH LINE
SAFETY PATH
VALIDATION
REGULATION
SCIENCE
SAFETY PATH
Material Characterization
#749
NAMs
#750
03:55:12
SANCE

Building a bridge between Annapolis 2023, Copenhagen 2024 and Copenhagen 2026

What have we learned in past meetings?

How are we moving the science forward at this meeting?

Are we moving the science forward?

Evidence-based toxicology

Copenhagen, 2024

Keynote: Evidence-Based Toxicology for Safety Assessment of Medical Devices. MMP as an example Thomas Hartung (Johns Hopkins Bloomberg School of Public Health, US)

Copenhagen, 2026

All presentations address evidence-based toxicology to some extent. "Science behind the standards"

Is it necessary to account for bioaccumulation when assigning a device to an exposure duration category?

Ron Brown, Principal Toxicologist, Risk Science Consortium, USA

Are we moving the science forward?

Improving the clinical relevance of test methods

Copenhagen, 2024

- Session: When All is Said and Done: Clinical Relevance of Biocompatibility Tests
  - Clinical Risk in the Real World - experience from 20000 implantable devices. Lars Magnus Bjursten (Convenor ISO 18562, Senior Professor of Bioimplant Research, SE)
  - Medical devices: adverse events, the skin and real world data Cecilia Svedman and Martin Mowitz (Skåne University Hospital Malmö, SE)

- Keynote: Using NAMs to improve clinical relevance of biological tests Helena Kandarova (Institute of Experimental Pharmacology and Toxicology, CEM, Slovak Academy of Sciences, SK)

Are we moving the science forward?

Improving the clinical relevance of test methods

Copenhagen, 2026

Emerging medical device allergens - an update from a clinical perspective

Cecilia Svedman, professor of Occupational and Environmental Dermatology IKVM, University of Lund, Sweden, Head of Department of Occupational and Environmental Dermatology, VOHRÖ, SUS Malmö, Sweden.

Martin Mowitz, chemist at the Department of Occupational and Environmental Dermatology at Skåne University Hospital, Lund University in Malmö, Sweden

Beyond biocompatibility: Integrating clinical evidence into Biological Evaluation across the Medical Device lifecycle

Jose Pablo Morales, MD, Chief Medical Officer, Veranex, USA

Are we moving the science forward?

Improving clinical relevance of test methods

Extraction

Copenhagen, 2024

- Support for simulated use extraction, and impact of degradation Ted Heise (Convenor 10993-18, MED Institute, US)
- Clinical relevance of extractions in biological tests Bob Przygoda (Adventure Biocompatibility Consulting, US)

Copenhagen, 2026

Overextraction and clinical relevance?

Speaker: Jianwei Li PhD, Chemistry Characterization Consultant and Technical Writer, Chemical Characterization Solutions, LLC, US

Are we moving the science forward?

Regulatory acceptance of NAMs

Copenhagen, 2024

Using NAMs to improve clinical relevance of biological tests

Helena Kandarova, Institute of Experimental Pharmacology and Toxicology, CEM, Slovak Academy of Sciences, SK

Copenhagen, 2026

Industry perspective/Case study - use of in vitro methods

Andy Forreryd, Key Account Manager & Scientific Liaison SenzaGen, Sweden

Practical challenges to the use of NAMs for medical devices – when state of the art science alone is not enough

Janine Townsend, Director at Chorley Consulting Ltd, UK

Are we moving the science forward?

Tiered approach

Copenhagen, 2024

ISO TC 194 Paris (21-25 Oct) preview including progress on the new Part 1

Jeremy Tinkler and Arthur Brandwood

Copenhagen, 2026

Introduction to panel: What information can be used to make a risk assessment supporting a step-wise approach?

Phil Clay, Senior Principal Toxicologist at Chorley Consulting Ltd, UK